VIA HAND DELIVERY NOVEMBER 15, 2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Kunsch et al.

Atty. Docket No.: PF198D1C1

Application Number: Unassigned

Group Art Unit: Unassigned

Filed: Herewith

Examiner: Unassigned

Title: Human Hepatoma-Derived Growth Factor-2

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir :

Prior to prosecution of the above-captioned application, Applicants respectfully request the entry of the following amendments. Applicants submit concurrently herewith (a) a Version With Markings To Show Changes Made; (b) a Request Under 37 C.F.R. § 1.821(e); and (c) a Submission of Formal Drawings.

Please enter the following amendments:

In the Specification:

At page 1, after the title and before the first full paragraph, please insert the following heading and paragraph:

Cross Reference to Related Applications

This application is a continuation of, and claims priority under 35 U.S.C. §120 to, U.S. Application Serial No. 09/263,625, filed March 5, 1999; which is a divisional of, and claims priority under 35 U.S.C. §120 to, U.S. Application Serial No. 08/464,600, filed June 5, 1995. Each of the above-referenced applications is hereby incorporated by reference in its entirety.

At page 1, before the first full paragraph, which begins "This invention relates to newly...", please insert the following heading:

Field of the Invention

At page 1, before the second full paragraph, which begins "Cell growth is regulated by …", please insert the following heading:

Background of the Invention

At page 4, before the first full paragraph, which begins "The following drawings are…", please insert the following heading:

Brief Description of the Drawings

At page 4, please delete the second full paragraph, which begins "Figures 1 depicts the…", and replace therewith the following paragraph:

Figures 1A-B depict the cDNA sequence (SEQ ID NO:1) and corresponding deduced amino acid sequence (SEQ ID NO:2) of HDGF-2. The standard one letter abbreviation for amino acids is used. Sequencing was performed using a 373 Automated DNA sequencer (Applied Biosystems, Inc.).

At page 4, please delete the fourth full paragraph, which begins "In accordance with an aspect…", and replace therewith the following paragraph:

In accordance with an aspect of the present invention, there is provided an isolated nucleic acid (polynucleotide) which encodes for the mature polypeptide having the deduced amino acid sequence of Figures 1A-B (SEQ ID NO:2) or for the mature polypeptide encoded by the cDNA of the clone deposited with the American Type Culture Collection (ATCC, located at 10801 University Boulevard, Manassas, Virginia 20110-2209) as ATCC Deposit No. 97163 on May 24, 1995.

At page 4, please delete the sixth paragraph, extending onto page 5, which begins "The polynucleotide of the present…", and replace therewith the following paragraph:

The polynucleotide of the present invention may be in the form of RNA or in the form of DNA, which DNA includes cDNA, genomic DNA, and synthetic DNA. The DNA may be double-stranded or single-stranded, and if single stranded may be the coding strand or non-coding (anti-sense) strand. The coding sequence which encodes the mature polypeptide may be identical to the coding sequence shown in Figures 1A-B (SEQ ID NO:1) or that of the deposited clone or may be a different coding sequence which coding sequence, as a result of the redundancy or degeneracy of the genetic code, encodes the same mature polypeptide as the DNA of Figures 1A-B (SEQ ID NO:1) or the deposited cDNA.

At page 5, please delete the first full paragraph, which begins "The polynucleotide which encodes...", and replace therewith the following paragraph:

The polynucleotide which encodes for the mature polypeptide of Figures 1A-B (SEQ ID NO:2) or for the mature polypeptide encoded by the deposited cDNA may include, but is not limited to: only the coding sequence for the mature polypeptide; the coding sequence for the mature polypeptide and additional coding sequence; the coding sequence for the mature polypeptide (and optionally additional coding sequence) and non-coding sequence, such as introns or non-coding sequence 5' and/or 3' of the coding sequence for the mature polypeptide.

At page 5, please delete the third full paragraph, which begins "The present invention further relates...", and replace therewith the following paragraph:

The present invention further relates to variants of the hereinabove described polynucleotides which encode for fragments, analogs and derivatives of the polypeptide having the deduced amino acid sequence of Figures 1A-B (SEQ ID NO:2) or the polypeptide encoded by the cDNA of the deposited clone. The variant of the polynucleotide may be a naturally occurring allelic variant of the polynucleotide or a non-naturally occurring variant of the polynucleotide.

At page 5, please delete the fourth full paragraph, which begins "Thus, the present invention includes ...", and replace therewith the following paragraph:

Thus, the present invention includes polynucleotides encoding the same mature polypeptide as shown in Figures 1A-B (SEQ ID NO:2) or the same mature polypeptide

encoded by the cDNA of the deposited clone as well as variants of such polynucleotides which variants encode for a fragment, derivative or analog of the polypeptide of Figures 1A-B or the polypeptide encoded by the cDNA of the deposited clone. Such nucleotide variants include deletion variants, substitution variants and addition or insertion variants.

At page 6, please delete the first full paragraph, which begins "As hereinabove indicated, the polynucleotide ...", and replace therewith the following paragraph:

As hereinabove indicated, the polynucleotide may have a coding sequence which is a naturally occurring allelic variant of the coding sequence shown in Figures 1A-B (SEQ ID NO:1) or of the coding sequence of the deposited clone. As known in the art, an allelic variant is an alternate form of a polynucleotide sequence which may have a substitution, deletion or addition of one or more nucleotides, which does not substantially alter the function of the encoded polypeptide.

At page 7, please delete the last paragraph, extending onto page 8, which begins "The present invention further relates ...", and replace therewith the following paragraph:

The present invention further relates to polynucleotides which hybridize to the hereinabove-described sequences if there is at least 70%, preferably at least 90%, and more preferably at least 95% identity between the sequences. The present invention particularly relates to polynucleotides which hybridize under stringent conditions to the hereinabove-described polynucleotides. As herein used, the term "stringent conditions" means hybridization will occur only if there is at least 95% and preferably at least 97% identity between the sequences. The polynucleotides which hybridize to the hereinabove described polynucleotides in a preferred embodiment encode polypeptides which either retain substantially the same biological function or activity as the mature polypeptide encoded by the cDNAs of Figures 1A-B (SEQ ID NO:1) or the deposited cDNA(s).

At page 9, please delete the first full paragraph, which begins "The present invention further relates ...", and replace therewith the following paragraph:

The present invention further relates to an HDGF-2 polypeptide which has the deduced amino acid sequence of Figures 1A-B (SEQ ID NO:2) or which has the amino acid

sequence encoded by the deposited cDNA, as well as fragments, analogs and derivatives of such polypeptide.

At page 9, please delete the second full paragraph, which begins "The terms 'fragment,' 'derivative' and ...", and replace therewith the following paragraph:

The terms "fragment," "derivative" and "analog" when referring to the polypeptide of Figures 1A-B (SEQ ID NO:2) or that encoded by the deposited cDNA, means a polypeptide which retains essentially the same biological function or activity as such polypeptide. Thus, an analog includes a proprotein which can be activated by cleavage of the proprotein portion to produce an active mature polypeptide.

At page 9, please delete the fourth full paragraph, which begins "The fragment, derivative or analog of...", and replace therewith the following paragraph:

The fragment, derivative or analog of the polypeptide of Figures 1A-B (SEQ ID NO:2) or that encoded by the deposited cDNA may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the mature polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) one in which the additional amino acids are fused to the mature polypeptide and employed for purification of the mature polypeptide. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

At page 32, please delete the second full paragraph, which begins "The DNA sequence encoding HDGF-2...", and replace therewith the following paragraph:

The DNA sequence encoding HDGF-2, ATCC No. 97163, is initially amplified using PCR oligonucleotide primers corresponding to the 5' sequences of the protein and the vector sequences 3' to the gene. Additional nucleotides corresponding to the gene are added to the 5' and 3' sequences respectively. The HDGF-2 5' oligonucleotide primer has the sequence 5' ACGT**GGATCC**GCGGCTGTGAGTCTGCGGCTCGGC 3' (SEQ ID NO:3)

contains a BamHI restriction enzyme site. The 3' sequence 5' CAAC**AAGCTT**TCACCTAGGAAGAAGGAGGTCTTCA 3' (SEQ ID NO:4) contains complementary sequences to a HindIII site and is followed by TGFa-HII coding sequence.

At page 33, please delete the first full paragraph, which begins "The DNA sequence encoding ...", and replace therewith the following paragraph:

The DNA sequence encoding the full length HDGF-2 protein, ATCC No. 97163, is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the gene:

At page 34, please delete the second full paragraph, extending onto page 35, which begins "The vector pA2 (modification of pVL941...", and replace therewith the following paragraph:

The vector pA2 (modification of pVL941 vector, discussed below) is used for the expression of the HDGF-2 protein using the baculovirus expression system (for review see: Summers, M.D. and Smith, G.E. 1987, A manual of methods for baculovirus vectors and insect cell culture procedures, Texas Agricultural Experimental Station Bulletin NO:1555). This expression vector contains the strong polyhedrin promoter of the Autographa californica nuclear polyhedrosis virus (AcMNPV) followed by the recognition sites for the restriction endonucleases. The polyadenylation site of the simian virus (SV)40 is used for efficient polyadenylation. For an easy selection of recombinant viruses the beta-galactosidase gene from E.coli is inserted in the same orientation as the polyhedrin promoter followed by the polyadenylation signal of the polyhedrin gene. The polyhedrin sequences are flanked at both sides by viral sequences for the cell-mediated homologous recombination of cotransfected wild-type viral DNA. Many other baculovirus vectors could be used in place of pA2 such as pRG1, pAc373, pVL941 and pAcIM1 (Luckow, V.A. and Summers, M.D., Virology, 170:31-39).

At page 35, please delete the first full paragraph, which begins "The plasmid is digested with ...", and replace therewith the following paragraph:

The plasmid is digested with the restriction enzymes and then dephosphorylated using calf intestinal phosphatase by procedures known in the art. The DNA is then isolated

from a 1% agarose gel using the commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.). This vector DNA is designated V2.

At page 37, please delete the first full paragraph, which begins "The plasmid construction strategy...", and replace therewith the following paragraph:

The plasmid construction strategy is described as follows:

At page 37, please delete the second full paragraph, which begins "The DNA sequence encoding HDGF-2,...", and replace therewith the following paragraph:

The DNA sequence encoding HDGF-2, ATCC No. 97163, contained in the plasmid vector pBluescript was amplified by PCR with a pBluescript vector primer (T3) at the 5' end and a HDGF-2 specific primer at the 3' end of the HDGF-2 coding sequence containing an XhoI restriction site. After amplification via PCR, the resultant PCR product is digested with BamHI and XhoI and ligated into a modified pcDNA-1 vector containing the HA tag in frame following the XhoI restriction site. The resultant plasmid contains the 5' untranslated region of HDGF-2 followed by the entire coding sequence fused in frame to the HA tag at the C-terminus.

In the Sequence Listing:

Please delete the original Sequence Listing (numbered pages 41-42) and renumber the Claims and Abstract (currently pages 43-46) as pages 41-44, respectively. Also, please append pages 1-7 of the Substitute Sequence Listing submitted herewith to the end of the present application.

In the Drawings:

Please replace the informal drawings of Figures 1 and 2 (3 sheets) with the Formal drawings of Figures 1A-1B and 2 (3 sheets) submitted herewith.

Statements Under 37 C.F.R. § 1.825(a) and (b)

Applicants herewith submit a paper copy of a Substitute Sequence Listing (6 pages) and, a computer-readable diskette containing the Substitute Sequence Listing. The Substitute Sequence Listing (paper copy and computer readable form (CRF)) is submitted herewith to comply with current format requirements under 37 C.F.R. § 1.823 and § 1.824.

As such, in accordance with 37 C.F.R. § 1.825(a), the undersigned attorney for Applicants hereby states that sequence information contained in the Substitute Sequence Listing submitted herewith is identical to the sequence information contained in the Substitute Sequence Listing submitted with original Application No. 08/464,600. The Substitute Sequence listing is completely supported by the specification as originally filed, and no new matter has been introduced.

In accordance with 37 C.F.R. § 1.825(b), the undersigned attorney for Applicants hereby states that the information in the paper copy of the Substitute Sequence Listing submitted herewith is identical to the information contained in the computer readable form of the Substitute Sequence Listing submitted herewith.

Remarks

The specification has been amended to add priority information and headings, to bring the references to Figures 1A-B in the specification into conformity with the formal drawings of Figures 1A-B submitted herewith, to add the American Type Culture Collection ("ATCC") accession number of the specified deposited plasmid, as well as the address for the ATCC, to correct minor typographical errors, and to bring the Sequence Listing into compliance. No new matter has been added by way of amendment to the specification.

Conclusion

Entry and consideration of the above amendments and remarks are respectfully requested.

Respectfully submitted,

Date: November 15, 2001

Jonathan L. Klein Reg. No. 41,119
Attorney for Applicants

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JLK/DS/ba

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

At page 4, the second full paragraph has been amended as follows:

Figures 1A-B depict the cDNA sequence (SEQ ID NO:1) and corresponding deduced amino acid sequence (SEQ ID NO:2) of HDGF-2. The standard one letter abbreviation for amino acids is used. Sequencing was performed using a 373 Automated DNA sequencer (Applied Biosystems, Inc.).

At page 4, the fourth full paragraph has been amended as follows:

In accordance with an aspect of the present invention, there is provided an isolated nucleic acid (polynucleotide) which encodes for the mature polypeptide having the deduced amino acid sequence of [Figure 1] Figures 1A-B (SEQ ID NO:2) or for the mature polypeptide encoded by the cDNA of the clone deposited [as ATCC Deposit No. on _____] with the American Type Culture Collection (ATCC, located at 10801 University Boulevard, Manassas, Virginia 20110-2209) as ATCC Deposit No. 97163 on May 24, 1995.

At page 4, the sixth paragraph, extending onto page 5, has been amended as follows:

The polynucleotide of the present invention may be in the form of RNA or in the form of DNA, which DNA includes cDNA, genomic DNA, and synthetic DNA. The DNA may be double-stranded or single-stranded, and if single stranded may be the coding strand or non-coding (anti-sense) strand. The coding sequence which encodes the mature

polypeptide may be identical to the coding sequence shown in [Figure 1] Figures 1A-B (SEQ ID NO:1) or that of the deposited clone or may be a different coding sequence which coding sequence, as a result of the redundancy or degeneracy of the genetic code, encodes the same mature polypeptide as the DNA of [Figure 1] Figures 1A-B (SEQ ID NO:1) or the deposited cDNA.

At page 5, the first paragraph has been amended as follows:

The polynucleotide which encodes for the mature polypeptide of [Figure 1] Figures 1A-B (SEQ ID NO:2) or for the mature polypeptide encoded by the deposited cDNA may include, but is not limited to: only the coding sequence for the mature polypeptide; the coding sequence for the mature polypeptide and additional coding sequence; the coding sequence for the mature polypeptide (and optionally additional coding sequence) and non-coding sequence, such as introns or non-coding sequence 5' and/or 3' of the coding sequence for the mature polypeptide.

At page 5, the third full paragraph has been amended as follows:

The present invention further relates to variants of the hereinabove described polynucleotides which encode for fragments, analogs and derivatives of the polypeptide having the deduced amino acid sequence of [Figure 1] Figures 1A-B (SEQ ID NO:2) or the polypeptide encoded by the cDNA of the deposited clone. The variant of the polynucleotide may be a naturally occurring allelic variant of the polynucleotide or a non-naturally occurring variant of the polynucleotide.

At page 5, the fourth full paragraph has been amended as follows:

Thus, the present invention includes polynucleotides encoding the same mature polypeptide as shown in [Figure 1] Figures 1A-B (SEQ ID NO:2) or the same mature polypeptide encoded by the cDNA of the deposited clone as well as variants of such polynucleotides which variants encode for a fragment, derivative or analog of the polypeptide of [Figure 1] Figures 1A-B or the polypeptide encoded by the cDNA of the deposited clone. Such nucleotide variants include deletion variants, substitution variants and addition or insertion variants.

At page 6, the first full paragraph has been amended as follows:

As hereinabove indicated, the polynucleotide may have a coding sequence which is a naturally occurring allelic variant of the coding sequence shown in [Figure 1] Figures 1A-B (SEQ ID NO:1) or of the coding sequence of the deposited clone. As known in the art, an allelic variant is an alternate form of a polynucleotide sequence which may have a substitution, deletion or addition of one or more nucleotides, which does not substantially alter the function of the encoded polypeptide.

At page 7, the last paragraph, extending onto page 8, has been amended as follows:

The present invention further relates to polynucleotides which hybridize to the hereinabove-described sequences if there is at least 70%, preferably at least 90%, and more preferably at least 95% identity between the sequences. The present invention particularly relates to polynucleotides which hybridize under stringent conditions to the hereinabove-described polynucleotides. As herein used, the term "stringent conditions" means hybridization will occur only if there is at least 95% and preferably at least 97% identity between the sequences. The polynucleotides which hybridize to the hereinabove described polynucleotides in a preferred embodiment encode polypeptides which either retain substantially the same biological function or activity as the mature polypeptide encoded by the cDNAs of [Figure 1] Figures 1A-B (SEQ ID NO:1) or the deposited cDNA(s).

At page 9, the first full paragraph has been amended as follows:

The present invention further relates to an HDGF-2 polypeptide which has the deduced amino acid sequence of [Figure 1] Figures 1A-B (SEQ ID NO:2) or which has the amino acid sequence encoded by the deposited cDNA, as well as fragments, analogs and derivatives of such polypeptide.

At page 9, the second full paragraph has been amended as follows:

The terms "fragment," "derivative" and "analog" when referring to the polypeptide of [Figure 1] Figures 1A-B (SEQ ID NO:2) or that encoded by the deposited cDNA, means a polypeptide which retains essentially the same biological function or activity as such

polypeptide. Thus, an analog includes a proprotein which can be activated by cleavage of the proprotein portion to produce an active mature polypeptide.

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The fragment, derivative or analog of the polypeptide of [Figure 1] Figures 1A-B (SEQ ID NO:2) or that encoded by the deposited cDNA may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the mature polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) one in which the additional amino acids are fused to the mature polypeptide and employed for purification of the mature polypeptide. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

At page 32, the second full paragraph has been amended as follows:

The DNA sequence encoding HDGF-2, ATCC [# ___] No. 97163, is initially amplified using PCR oligonucleotide primers corresponding to the 5' sequences of the protein and the vector sequences 3' to the gene. Additional nucleotides corresponding to the gene are added to the 5' and 3' sequences respectively. The HDGF-2 5' oligonucleotide primer has the sequence 5' ACGT**GGATCC**GCGGCTGTGAGTCTGCGGCTCGGC 3' (SEQ ID NO:3) contains a BamHI restriction enzyme site. The 3' sequence 5' CAAC**AAGCTT**TCACCTAGGAAGAAGGAGGTCTTCA 3' (SEQ ID NO:4) contains complementary sequences to a HindIII site and is followed by TGFa-HII coding sequence.

At page 33, the first full paragraph has been amended as follows:

The DNA sequence encoding the full length HDGF-2 protein, ATCC [#___] No. 97163, is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the gene:

At page 34, the second full paragraph, extending onto page 35, has been amended as follows

The vector pA2 (modification of pVL941 vector, discussed below) is used for the expression of the HDGF-2 protein using the baculovirus expression system (for review see: Summers, M.D. and Smith, G.E. 1987, A manual of methods for baculovirus vectors and insect cell culture procedures, Texas Agricultural Experimental Station Bulletin NO:1555). This expression vector contains the strong polyhedrin promoter of the Autographa californica nuclear polyhedrosis virus (AcMNPV) followed by the recognition sites for the restriction [endonucleases .] endonucleases. The polyadenylation site of the simian virus (SV)40 is used for efficient polyadenylation. For an easy selection of recombinant viruses the beta-galactosidase gene from E.coli is inserted in the same orientation as the polyhedrin promoter followed by the polyadenylation signal of the polyhedrin gene. The polyhedrin sequences are flanked at both sides by viral sequences for the cell-mediated homologous recombination of cotransfected wild-type viral DNA. Many other baculovirus vectors could be used in place of pA2 such as pRG1, pAc373, pVL941 and pAcIM1 (Luckow, V.A. and Summers, M.D., Virology, 170:31-39).

At page 35, the first full paragraph has been amended as follows

The plasmid is digested with the restriction [enzymes and] enzymes and then dephosphorylated using calf intestinal phosphatase by procedures known in the art. The DNA is then isolated from a 1% agarose gel using the commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.). This vector DNA is designated V2.

At page 37, the first full paragraph has been amended as follows:

The plasmid construction strategy is described as [follow] follows:

At page 37, the second full paragraph has been amended as follows

The DNA sequence [encoidng] encoding HDGF-2, ATCC [# ____] No. 97163, contained in the plasmid vector pBluescript was amplified by PCR with a pBluescript vector primer (T3) at the 5' end and a HDGF-2 specific primer at the 3' [endo] end of the HDGF-2 coding sequence containing an XhoI restriction site. After amplification via PCR, the resultant PCR product is digested with BamHI and XhoI and ligated into a modified pcDNA-

1 vector containing the HA tag in frame following the XhoI [restricition] restriction site. The resultant plasmid contains the 5' untranslated region of HDGF-2 followed by the entire coding sequence fused in frame to the HA tag at the C-terminus.

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SUBMISSION OF SUBSTITUTE/FORMAL DRAWINGS

Commissioner For Patents
Washington, D.C. 20231

ATTN: Official Draftsperson

Sir:

Applicants submit herewith Formal Drawings of Figures 1A-1B and 2 (3 sheets) to replace the informal drawings of Figures 1 and 2 (3 sheets) as originally filed.

No fee is believed due for this submission. In the event that a fee is required in connection with this submission, please charge the required fee to Deposit Account No. 08-3425.

Respectfully submitted,

Date: NOVEMBER 15, 2001

Jonathan L. Klein Reg. No. 41,119
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KKH/JLK/DS/ba

NUCLEOTIDE AND PREDICTED TRANSLATION PRODUCT
FOR HUMAN HEPATOMA DERIVED GROWTH FACTOR-LIKE PROTEIN (HDGF-2)

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   1  GAATTCGTGCTCTTAGGGTGGTTGGGTGGTAAGATGGCGGCTGTGAGTCTGCGGCTCGGC
                                      M  A  A  V  S  L  R  L  G
  61  GACTTGGTGTGGGGGAAACTCGGCCGATATCCTCCTTGGCCAGGAAAGATTGTTAATCCA
      D  L  V  W  G  K  L  G  R  Y  P  P  W  P  G  K  I  V  N  P
 121  CCAAAGGACTTGAAGAAACCTCGCGGAAAGAAATGCTTCTTTGTGAAATTTTTTGGAACA
      P  K  D  L  K  K  P  R  G  K  K  C  F  F  V  K  F  F  G  T
 181  GAAGATCATGCCTGGATCAAAGTGGAACAGCTGAAGCCATATCATGCTCATAAAGAGGAA
      E  D  H  A  W  I  K  V  E  Q  L  K  P  Y  H  A  H  K  E  E
 241  ATGATAAAAATTAACAAGGGTAAACGATTCCAGCAAGCGGTAGATGCTGTCGAAGAGTTC
      M  I  K  I  N  K  G  K  R  F  Q  Q  A  V  D  A  V  E  E  F
 301  CTCAGGAGAGCCAAAGGGAAAGACCAGACGTCATCCCACAATTCTTCTGATGACAAGAAT
      L  R  R  A  K  G  K  D  Q  T  S  S  H  N  S  S  D  D  K  N
 361  CGACGTAATTCCAGTGAGGAGAGAAGTAGGCCAAACTCAGGTGATGAGAAGCGCAAACTT
      R  R  N  S  S  E  E  R  S  R  P  N  S  G  D  E  K  R  K  L
 421  AGCCTGTCTGAAGGGAAGGTGAAGAAGAACATGGGAGAAGGAAAGAAGAGGGTGTCTTCA
      S  L  S  E  G  K  V  K  K  N  M  G  E  G  K  K  R  V  S  S
 481  GGCTCTTCAGAGAGAGGCTCCAAATCCCCTCTGAAAAGAGCCCAAGAGCAAAGTCCCCGG
      G  S  S  E  R  G  S  K  S  P  L  K  R  A  Q  E  Q  S  P  R
 541  AAGCGGGGTCGGCCCCCAAAGGATGAGAAGGATCTCACCATCCCGGAGTCTAGTACCGTG
      K  R  G  R  P  P  K  D  E  K  D  L  T  I  P  E  S  S  T  V
 601  AAGGGGATGATGGCCGGACCGATGGCCGCGTTTAAATGGCAGCCAACCGCAAGCGAGCCT
      K  G  M  M  A  G  P  M  A  A  F  K  W  Q  P  T  A  S  E  P
 661  GTTAAAGATGCAGATCCTCATTTCCATCATTTCCTGCTAAGCCAAACAGAGAAGCCAGCT
      V  K  D  A  D  P  H  F  H  H  F  L  L  S  Q  T  E  K  P  A
 721  GTCTGTTACCAGGCAATCACGAAGAAGTTGAAAATATGTGAAGACCTCCTTCTTCCTAGG
      V  C  Y  Q  A  I  T  K  K  L  K  I  C  E  D  L  L  L  P  R
 781  TGAAGTGGGCAATGCAGCCAAGATGATGCTGATCGTGAACATGGTCCAAGGGAGCTTCAT
 841  GGCCACTATTGCCGAGGGGCTGACCCTGGCCCAGGTGACAGGCCAGTCCCAGCAGACACT
 901  CTTGGACATCCTCAATCAGGGACAGTTGGCCAGCATCTTCCTGGACCAGAAGTGCCAAAA
 961  TATCCTGCAAGGAAACTTTAAGCCTGATTTCTACCTGAAATACATTCAGAAGGATCTCCG
1021  CTTAGCCATTGCGCTGGGTGATGCGGTCAACCATCCGACTCCCATGGCAGCTGCAGCAAA
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FIG. 1A

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1081  TGAGGTGTACAAAAGAGCCAAGGCGCTGGACCAGTCTGACAACGATATGTCCGCCGTGTA
1141  CCGAGCCTACATACACTAAGCTGTCGACACCCCGCCCTCACCCCTCCAATCCCCCCTCTG
1201  ACCCCCTCTTCCTCACATGGGGTCGGGGGCCTGGGAGTTCATTCTGGTACCAGCCCACCT
1261  ATCTCCATTTCCTTTTATACAGACTTTGAGACTTGCCATCAGCACAGCACACAGCAGCAC
1321  CCTTCCCCTGAGGTCGGTGGGGAGGGGACAAGTGTCAGCAGGATTGGCGTGTGGGAAAGC
1381  TCTTGAGCTGGGCACTGGCCCCCCGGACGAGGTGGYTGTGTGTTCACACACACACACACA
1441  CACACACACACACACACACACACAGGCTCTCGCCCCAGGATAGAAGCTGCCCAGAAACTG
1501  CTGCCTGGCTTTTTTTCTTCCGAGCTTGTCTTATCTCAAACCCCTTCCAGTCAAGGAACT
1561  AGAATCAGCAACGAGAGTTGGAAGCCTTCCCACAGCTTCCCCCAGAGCGAAGAGGCTGTA
1621  GTCATGTCCCCATCCCCCACTGGATTCCCTACAAGGAGAGGCCTTGGGCCCAGATGAGCC
1681  AGTACAGACTCCAGACAGAGGGGCCCTTGGGGCCCTCCAACCTCAGGTGATGAGCTGAGA
1741  AAGATGTTCACGTCTAAGCGTCCAGTGTGCACCCAGCGCTCCATAGACGCCTTTGTGAAC
1801  TGAAAAGAGACTGGCAGAGTCCCGAGAAGATGGGGCCCTGGCTTTCCAGGGAGTGCAGCA
1861  AGCAGCCGGCCTGCAGGTGAGCATGGAGGCCCGGCCCTCACCGCCTCGAAGCCATGCCCC
1921  AGATGCCACTGCCACAGCGGGCGCTCGCTCCTCCCTAGGCTGTTTTAGTATTTGGATTTG
1981  CATTCCATCCCTTGGGAGGGAGTCCTCAGGGCCACTAGTGATGAGCCAAGAGGAGTGGGG
2041  GTTGGGGGCGCTCCTTTCTGTTTCCGTTAGGCCACAGACTCTTCACCTGGCTCTGACTTA
2101  CCTCGGTCCCCTCCCAGTGGTCCCACCTTCTCCACCCTGCCCTGCCAAGTCCCCTGCATG
2161  CCCACCGCTCTCCATCCTCCCTCCTCTCCCTCTTCCTCCCGTGGAGACAGTATTTCTTTC
2221  TGTCTGTCCCTTTGGCCCAGACCCAGCCTGACCAACGATGAGCATTTCTTAGGCTCAGCT
2281  CTTGATACGGAAACGAGTGTCTTCACTCCAGCCAGCATCATGGTCTTCGGTGCTTCCCGG
2341  GCCCGGGGTCTGTCGGGAGGGAAGAGAACTGGGCCTGACCTACCTGAACTGACTGGCCCT
2401  CCGAGGTGGGTCTGGGACATCCTAGAGGCCCTACATTTGTCCTTGGATAGGGGACCGGGG
2461  GGGGCTTGGAATGTTSCAAAAAAAAAAGTTACCCAAGGGATGTCAGTTTTTTATCCCTCT
2521  GCATGGGTTGGATTTTCCAAAATCATAATTTGCAGAAGGAAGGCCAGCATTTACGATGCA
2581  ATATGTAATTATATATAGGGTGGCCACACTAGGGCGGGGTCCTTCCCCCCTCACAGCTTT
2641  GGCCCCTTTCAGAGATTAGAAACTGGGTTAGAGGATTGCAGAAGACGAGTGGGGGGAGGG
2701  CAGGGAAGATGCCTGTCGGGTTTTTAGCACAGTTCATTTCACTGGGATTTTGAAGCATTT
2761  CTGTCTGAACACAAAGCCTGTTCTAGTCCTGGCGGAACACACTGGGGGTGGGGGCGGGGG
2821  AAGATGCGGTAATGAAACCGGTTAGTCAATTTTGTCTTAATATTGTTGACAATTCTGTAA
2881  AGTTCCTTTTTATGAATATTTCTGTTTAAGCTATTTCACCTTTCTTTTGAAATCCTTCCC
2941  TTTTAAGGAGAAAATGTGACACTTTGTGAAAAAGCTTGTAAGAAAGCCCCTCCCTTTTTT
3001  CTTTAAACCTTTAAATGACAAATCTAGGTAATTAAGGTTGTGAATTTTTATTTTTGCTTT
3061  GTTTTTAATGAACATTTGTCTTTCAGAATAGGATTGTGTGATAATGTTTAAATGGSAAAA
3121  ACAAAACATGATTTTGTGCAATTAACAAAGCTACTGCAAGGAAAATAAAACACTTCTTGG
3181  TAACAAAAAAAAAAAAAAAAA  3202
```

FIG. 1B

COMPARISON OF AMINO ACID SEQUENCES
BETWEEN HDGF-1 AND HDGF-2

```
                                        10        20        30
HDGF-2                                  MAAVSLRLGDLVWGKLGRYPPWPGKIVNPPKDLKKPRG
                                        ||||::|:  ||:||::| : |::  |: :
HDGF-1                                  MSRSNRQKEYKCGDLVFAKMKGYPHWPARIDEMPEAAVKSTA

            40        50        60        70        80        90
HDGF-2      KKCFFVKFFGTEDHAWIKVEQLKPYHAHKEEMIKINKGKRFQQAVDAVEEFLRRAKGKDQ
            :| : | ||||:: |::  ::| ||:: ||:: | || | | ::: ::|:     : : :
HDGF-1      NK-YQVFFFGTHETAFLGPKDLFPYEESKEKFGKPNKRKGFSEGLWEIEN-----NPTVK

            100       110       120       130       140       150
HDGF-2      TSSHNSSDDKNRRNSSEERSRPNSGDEKRKLSLSEGKVKKNMGEGKKRVSSGSSERGSKS
            :|:::||::|:  :::|  : :::||:::| : :||: :   :|||  ::: ::|:::|:
HDGF-1      ASGYQSSQKKSCVEEPEPEPEAAEGDGDKK-GNAEGSSD---EEGKLVIDEPAKEKNEKG

            160       170       180       190       200       210
HDGF-2      PLKRAQEQSPRKRGRPPKDEKDLTIPESSTVKGMMAGPMA-AFKWQPTASEPVKDADPHF
            :||| :::   :: ::||:::: :  |:::::  :: |:: : : ::|:|||| :: :|:
HDGF-1      ALKRRAGDLLEDSPKRPKEAENPEGEEKEAATLEVERPLPMEVEKNSTPSEPGSGRGPPQ

            220       230       240       250
HDGF-2      HHFLLSQTEKPAVCYQAITKKLKICEDLLLPR

HDGF-1      EEEEEEDEEEEATKEDAEAPGIRDHESL
```

FIG. 2